Remarks

Claim Objections

The Examiner has objected to Claims 13 and 18 as being dependent from rejected base claims. While Applicant appreciates the implication that these claims would be allowable if rewritten to include the limitations of the claims from which they depend, Applicant has not made such an amendment and asserts that, for all of the reasons set forth below, these claims are allowable in their present form. Applicant also notes that the Examiner indicates that these claims are dependent from rejected claims 1-3. In fact, claims 13 and 18 were amended in the Request for Continued Examination filed July 3, 2006. Claim 13 was amended to depend from currently pending claim 2, while claim 18 was amended to depend from currently pending claim 2 or 3. Claims 13 and 18 therefore do not depend from claim 1.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 2-4, 14-17, 19-22 and 27-31 under 35 U.S.C. §112, First Paragraph, asserting that these claims lack both written description and enablement. These rejections are respectfully traversed.

Written description

The Examiner asserts that Applicant claims a genus of methods drawn to the use of any "archaeon Family B DNA polymerase" and interprets this

phrase to broadly encompass variants and mutants of naturally occurring archaeon Family B DNA polymerases.

As an initial matter, Applicant notes that present independent claims 2 and 3 encompass only those archaeon Family B DNA polymerases that *both* (i) are encoded by a nucleic acid that either hybridizes under stringent conditions (claim 2) or exhibits a defined amino acid sequence identity (claim 3) to wild type Vent DNA polymerase; *and* (ii) have the ability to incorporate acyclonucleotides. Such DNA polymerases are well described in the application; present claims 2 and 3 meet the Written Description requirement

As the Examiner is aware, the Written Description requirement ensures that patent applicants claim subject matter that was "within the possession of the inventors" See e.g., Fujikawa v. Wattanasin, 39 USPQ2d 1895, 1904 (Fed. Cir. 2000) "...*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the *disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question*." (emphasis added). Certain court decisions have clarified what is required to satisfy the written description requirement for enzymatic proteins (and their use). Furthermore, the Patent Office's own Written Description Guidelines provide illustrative examples of claim language for proteins that satisfy the Written Description requirement. Even a cursory review of the relevant cases and Guidelines demonstrates that the present claims are patentable.

One Federal Circuit case that addresses a situation closely analogous to the present one is *Invitrogen Corp. v. Clonetech Labs. Inc.*. 77 USPQ2d 1161 (Fed. Cir. 2005). The claims at issue in *Invitrogen* were to a reverse

transcriptase ("RT") enzyme modified such that it lacks RNase H activity. The specification provided only one representative species. The court nonetheless found the claims adequately described. The court emphasized that at the time of the invention, the sequences of RT genes were known and members of the RT gene family shared significant homologies from one species of RT to another. The court also emphasized that "the specification also discloses test data that the enzyme produced by the listed sequence has the claimed features - DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient." Id. at 1176. Thus, under *Invitrogen*, a claim to an enzymatic protein satisfies the written description requirement when members of the protein/gene family are known and are known to share homologies, and the specification provides a single example of a member species with the relevant enzymatic activity.

The present situation more than satisfies these requirements. The Examiner does not dispute that members of the family have homology. Indeed, the present specification specifically exemplifies a number of species of archaeon Family B polymerases that exhibit significant identity and similarity to each other at the amino acid level, and are demonstrably different at the amino acid level than non-archaeon Family B polymerases. As can be seen in Table 3, archaeon Family B polymerases exhibit a high degree of identity and similarity over the entire protein with the Motif B region sharing almost complete identity between the different archaeon DNA polymerases listed. Additionally, Table 3 lists several non-archaeon Family B polymerases, each of which exhibits decreased sequence conservation over the Motif B region, as well as two non-family B polymerases, each of which

exhibits a complete lack of sequence conservation over this region. Furthermore, the structural conservation of this genus is shown in Example 10, which demonstrates that a corresponding mutation in a corresponding amino acid residue of the Motif B region of two members of the genus leads to a similar modification of acyclonucleotide incorporation efficiency. Therefore, the first requirement of *Invitrogen* is fully satisfied in the present case.

The second requirement of *Invitrogen* is also satisfied. The present specification includes not one but at least seven examples archaeon Family B polymerases that exhibit the claimed acyclonucleotide incorporation properties. For example, Example 5 shows that wild type Vent(exo$^-$) DNA polymerase incorporates dye-acyclo-CTP more efficiently than dye-ddCTP. Example 6 shows that three additional archaeon Family B polymerases incorporate dye-acyclo-CTP with an efficiency comparable to that of Vent(exo-) DNA polymerase seen in Example 5. Also, Example 10 illustrates that two different variant archaeon Family B polymerases also have the claimed activity. Indeed, Example 10 shows that comparable sequence variations achieve comparable activity adjustments. The specification thus amply illustrates examples of proteins having the claimed structural features (sequence and/or hybridization) also have the claimed activity, more than satisfying the second *Invitrogen* requirement.

It is therefore clear that, under the relevant case law, the present claims satisfy the Written Description requirement.

A review of the Patent Office Written Description guidelines confirms the patentability of the present claims. Particularly relevant portions of the Written Description guidelines are Examples 9 and 14. Example 9 presents

a patentable structure for claims that recite hybridization conditions. In that Example, a claim reciting "An isolated nucleic acid that specifically hybridizes under highly stringent conditions to... [the described sequence], wherein said nucleic acid encodes a protein [having a particular function]..." is said to satisfy the written description requirement when the specification recited only a single nucleotide sequence encoding a protein with the recited function. Indeed, Example 9 states that:

> "...a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of the DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention."

Present claim 2 has precisely the same structure as recommended in Example 9 of the Written Description guidelines. Furthermore, present claim 2 is supported by a specification containing not one, but at least *six* different specific examples of proteins encoded by sequences that hybridize under the recited conditions to the recited example sequence, which proteins also have the recited sequence. Present claim 2 therefore more than satisfies the Written Description requirements set forth in the Patent Office's own guidelines.

Example 14 of the Written Description guidelines presents a patentable structure for claims that recite proteins based on their function and degree of homology. In that Example, a claim reciting "A protein having SEQ ID NO: 3 and variants thereof that are a least 95% identical to SEQ ID NO: 3

and catalyze the reaction of A → B" is said to satisfy the written description requirement when the specification recites only a single polypeptide sequence encoding a protein with the recited function.

Present claim 3 has precisely the same structure as recommended in Example 14 of the Written Description guidelines. The degree of identity recited in claim 3 is lower than that in Example 14. However, claim 3 is supported by a specification containing not one, but at least *seven* different specific examples of proteins having the recited degree of identity and the recited activity. Moreover, the recited relationship between degree of identity and activity is further supported by a sworn Declaration. Under these circumstances, it is clear that present claim 3 satisfies the Written Description requirement as exemplified by Example 14 of the Patent Office Written Description guidelines.

For all of these reasons, it is clear that the present claims satisfy the Written Description requirement, and particularly that they satisfy the standards set out in the case law and in the Patent Office Written Description guidelines. Applicant has previously made similar points, and in particular has discussed the high degree of sequence homology among archaeon Family B polymerases, and the relationship between this homology and their activity. Moreover, Applicant has submitted a Declaration in support of these points.

The Examiner has rejected these arguments, however. The Examiner has taken the position that the Written Description requirement is satisfied only for those DNA polymerases whose activity is specifically exemplified in the application (i.e., Vent, Deep Vent, Pfu, 9°N and the specifically disclosed variants). This is not the law, nor should it be.

The Examiner has stated that "applicants reasoning that the degree of homogeneity between these polymerases would or should afford certain polymerase properties is not persuasive" apparently because some DNA polymerases may have a high degree of homogeneity even though not all share the same activity.

This point is flawed for several reasons. First, the present claims are limited only to polymerases that do in fact share both sequence homology and activity.

Second, the Examiner is not entitled to ignore the sworn Declaration of an expert in the field definitively stating that there *is* a relationship between structural homogeneity and functional activity. The case law is clear with regard to an Examiner's proper consideration of declaratory evidence relating to Written Description. For example, in As stated in *In re Alton*, the application claimed an analog of a polypeptide that was similar, but not identical, to a polypeptide disclosed in the specification. As in the present situation, the claims were rejected for lack of written description and a declaration was submitted to provide evidence that one of ordinary skill in the art would consider the description sufficient to show that the applicant had possession of the claimed analog. The Federal Circuit concluded that the Examiner improperly dismissed the declaration of person skilled in art without adequate explanation of how declaration failed to overcome the rejection. The same is true here.

In the Office Action, the Examiner acknowledges submission of the Declaration but does not address why the points made in the Declaration do not overcome the rejection. The Declaration attests to the fact that a high degree of primary amino acid and three dimensional structural conservation

is observed between archaeon Family B DNA polymerases. The Declaration further provides evidence in the form of peer-reviewed scientific literature demonstrating this high degree of structural conservation, as well as a physical explanation for the preferential incorporation of acyclonucleotides by members of this genus. Additionally, the Declaration submits further data confirming that the structure-function relationship described in the application extends to other members of the claimed genus of archaeon Family B DNA polymerases that share at least 30% primary amino acid sequence identity with Vent DNA polymerase. Each of these points alone would be sufficient to overcome the rejection. Together, they are unassailable.

Finally, there is no legal requirement that an Applicant demonstrate that *all* members of a family necessarily have a given activity in order to write a claim to those members that do. As held in *Invitrogen*, so long as a *single member* of the recited structural class has the activity, the claim satisfies the Written Description requirement.

The Examiner has also asserted that the Applicant has not established a structure-function relationship of archaeon Family B polymerases with respect to incorporation of acyclonucleotides into a DNA fragment (although the Examiner acknowledges that such a relationship exists with respect to polymerase function generally). This assertion is incorrect.

As discussed above, the case law and the Written Description guidelines clearly set forth the requirements for establishing a correlation between sequence and function. The present application goes *well beyond* those requirements in providing *explicit exemplification* of *several* proteins

having the recited sequence characteristics that also have the recited activity.

The Examiner is simply mistaken and the rejection should be removed.

Thus, for all of the reasons set forth above, it is clear that the present claims meet the Written Description requirement, and that the Examiner's rejection of these claims is flawed. Moreover, Applicants point out that the patent statute itself *requires* that the present claim language be presumed to have satisfied the statutory requirements of patentability, including both written description and enablement. Specifically, 35 U.S.C. § 282 states: "A patent shall be presumed valid". The hybridization language present in claim 2 is identical to language in issued United States patent number 5,500,363, and therefore must be presumed to be patentable.

Enablement

The Examiner asserts that the specification, while being enabling for methods of site-specific incorporation of acyclonucleotides into DNA comprising reacting certain disclosed archaeon Family B polymerases with a primed DNA template, does not provide enablement for methods of site-specific incorporation of acyclonucleotides into DNA comprising reacting any archaeon Family B polymerase with a primed DNA template. In rejecting the claims for lack of enablement, the Examiner relies on the broad interpretation of archaeon Family B DNA polymerases discussed above, asserting that the specification does not provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. Applicant traverses this rejection for the following reasons:

The arguments presented above relating to the written description requirement are reiterated here in their entirety as they relate to the enablement determination. Specifically, Applicant submits that one of ordinary skill in the art would understand upon reading the application that the Applicant had possession of the genus of archaeon Family B DNA polymerases, as well as the structure-function relationship that would permit one of ordinary skill in the art to recognize archaeon Family B DNA polymerases that share the ability to incorporate acyclonucleotides into a DNA fragment.

The Federal Circuit has identified several non-limiting factors that inform an enablement determination. See In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Although these factors are non-limiting, they nevertheless provide a satisfactory framework to demonstrate that the presently claimed invention is enabled by the specification. Thus, Applicant addresses these factors as they relate to the claimed invention. The Wands factors are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of one of ordinary skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The existence of working examples; and
8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

(1-2) The breadth of the claims and nature of the invention:

The presently pending claims recite methods of site-specific incorporation of acyclonucleotides into DNA comprising reacting an archaeon

Family B DNA polymerase with a primed DNA template and a nucleotide solution containing at least one acyclonucleotide to produce fragments of DNA with the acyclonucleotide covalently attached to the 3' terminal residue. Applicant submits that the general nature of the claimed invention, i.e. reacting a polymerase with a primed template and nucleotides to generate an extension product, is well within the ordinary skill in the art.

The presently pending claims specifically recite methods comprising reacting an archaeon Family B DNA polymerase with a primed DNA template and a nucleotide solution containing at least one acyclonucleotide, wherein the archaeon Family B DNA polymerase either hybridizes in a Southern blot to one of several isolated DNA fragments of SEQ ID NO:4 under stringent hybridization conditions, or shares at least 30% primary amino acid sequence identity with Vent DNA polymerase, and wherein the polymerase is capable of incorporating an acyclonucleotide. Thus, the currently pending claims are not directed to methods comprising reacting <u>any polymerase</u> with the other recited components, only the genus of archaeon Family B DNA polymerases. As described above, the specification describes the genus of archaeon Family B DNA polymerases with sufficient particularity such as to provide sufficient guidance to enable those of ordinary skill in the art to practice the claimed invention.

<u>(3 and 5) The state of the prior art and the level of predictability in the art:</u>

Numerous DNA polymerases are known in the prior art. Additionally, the primary amino acid sequence of a given DNA polymerase very often

allows one of ordinary skill in the art to classify that polymerase into one of several families (see page 3 of the application, lines 8-17).

As described in detail above, the specification describes a family of archaeon Family B DNA polymerases, as well as a structure-function relationship between the primary amino acid sequence of the archaeon Family B DNA polymerases and their capacity to incorporate acyclonucleotides into a DNA fragment (see, e.g., Table 3 and Examples 5, 6 and 10). Additionally, in the Declaration, evidence was submitted showing a high degree of primary amino acid and three dimensional structural conservation between archaeon Family B DNA polymerases, as well as a physical explanation for the preferential incorporation of acyclonucleotides by members of this genus. Furthermore, experimental data was submitted confirming that the structure-function relationship described in the application between members of the claimed genus and their ability to utilize acyclonucleotides as substrates extends to other members of the genus.

Thus, far from being an unpredictable field, Applicant submits that the state of the prior art and the level of predictability in the art are sufficient to enable one of ordinary skill in the art to practice the claimed invention.

(4) The level of one of ordinary skill:

The skill level of one of ordinary skill in the art is high, most likely at the Ph.D. level.

(6 and 7) The amount of direction provided by the inventor and the existence of working examples:

The specification must be read from the point of view of one skilled in the art. *See Alton*, 37 USPQ2d at 1584. Those of ordinary skill in the art are well versed in identifying and classifying polypeptides, including DNA polymerases, based on their primary amino acid sequence. As explained in detail above, the specification describes a family of archaeon Family B DNA polymerases, as well as a structure-function relationship between the primary amino acid sequence of the archaeon Family B DNA polymerases and their capacity to incorporate acyclonucleotides into a DNA fragment. Furthermore, as explained in detail above, the specification provides four working examples of members of the genus of archaeon Family B DNA polymerases, derived from different species, that exhibit similar abilities to incorporate acyclonucleotides into a DNA fragment (see, e.g., Table 3 and Examples 5, 6 and 10).

In *Invitrogen*, the Federal Circuit held that, "the scope of enablement... is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *Invitrogen* at 1173 (quoting *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196). Applicant thus submits that the description provided by the specification and the level of ordinary skill in the art are sufficient to enable one of ordinary skill in the art to practice the claimed invention.

(8) The quantify of experimentation needed to make or use the invention based on the content of the disclosure

The quantity of experimentation needed to make or use the claimed invention, is neither excessive nor outside the skill set of one skilled in the

art. To practice the claimed invention, one of ordinary skill in the art reacts an archaeon Family B DNA polymerase with a primed DNA template and a nucleotide solution containing at least one acyclonucleotide.

As described in detail above, the specification describes a family of archaeon Family B DNA polymerases, as well as a structure-function relationship between the primary amino acid sequence of the archaeon Family B DNA polymerases and their capacity to incorporate acyclonucleotides into a DNA fragment (see, e.g., Table 3 and Examples 5, 6 and 10). Thus, given only the primary amino acid sequence of a DNA polymerase, one of ordinary skill in the art will very often be able to determine whether that polymerase can be used in accordance with the currently pending claims without any experimentation other than an *in silico* BLAST search.

Furthermore, in the rare instance where it cannot be determined whether a DNA polymerase belongs to the genus of archaeon Family B DNA polymerases recited in the currently pending claims, one of ordinary skill in the art would be able to determine with a simple assay whether that polymerase is capable of incorporating acyclonucleotides such that it can be used in accordance with the currently pending claims. In fact, the specification provides a description of such an assay in Example 1, entitled "A titration assay to measure the relative efficiency of modified nucleotide incorporation". Applicant notes that the description of this assay was sufficient to overcome a previously levied rejection asserting that the specification was not enabling for a method of testing a DNA polymerase for efficacy of incorporation of modified nucleotides. Thus, the description of this assay is surely sufficient to enable one of ordinary skill in the art to

determine whether a given polymerase is capable of incorporating acyclonucleotides such that it can be used in accordance with the currently pending claims.

As stated in *Wands*, "Enablement is not precluded by the necessity for some experimentation such as *routine* screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" *Wands* at 1404 (emphasis added). Thus, in contrast to the Examiner's assertion, given the high level of predictability based on the primary amino acid sequence as well as the extensive guidance provided in the specification for determining whether a particular DNA polymerase may be used in according with the currently pending claims, the quantity of experimentation needed to make or use the claimed invention is neither excessive nor undue.

Applicant thus requests that the rejection of the currently pending claims for lack of enablement be withdrawn.

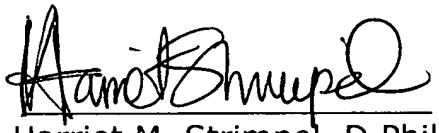
CONCLUSION

Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants petition for a 2-month extension of time and submit check in the amount of $225 for the extension fees. Please charge Deposit Account No. 14-0740 for any deficiencies.

Respectfully submitted,

NEW ENGLAND BIOLABS, INC.



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